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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/328,975	06/09/99	WOLFF J	MIRUS009

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MARK K JOHNSON
P O BOX 510644
NEW BERLIN WI 53131-0644

EXAMINER	
SCHNIZER,R	
ART UNIT	**PAPER NUMBER**
1632	7

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

FILE COPY

Office Action Summary	Application No. 09/328,975	Applicant(s) Wolff
	Examiner Richard Schnizer	Group Art Unit 1632

☐ Responsive to communication(s) filed on _____

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claim

☒ Claim(s) *1-18* is/are pending in the applicat

Of the above, claim(s) _____ is/are withdrawn from consideration

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-18* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☒ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). 2

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

— SEE OFFICE ACTION ON THE FOLLOWING PAGES —

DETAILED ACTION

Applicant's elections without traverse of the species "pegylated derivatives" in Paper No. 4, and of "succinylated PLL" in Paper No. 6 are acknowledged.

Claims 1-18 are pending in the application, and are under consideration in this office action.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-18 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a process for delivering to a cell *in vitro* a complex comprising a polyion, a polymer, and a charged polymer, wherein either the polyion, the polymer, or the charged polymer comprises a nucleic acid; and while being enabling for a complex for delivering a polyion to a cell *in vitro* wherein the polyion is complexed with a charged polymer, and wherein either the polyion or the polymer comprises a nucleic acid, does not reasonably provide enablement for any complex which does not comprise a nucleic acid, or for delivery of any complex *in vivo*, or for any drug. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The asserted utility of the invention is the delivery of particles such as molecules, polymers, nucleic acids, and genes to cells. See page 1, lines 14-16. The scope of the invention encompasses delivery to cells *in vitro* and *in vivo*. See page 14, lines 10-12.

With respect to the scope of molecules which may be delivered by the invention, the claims encompass the delivery of any polymer. The term "polymer" encompasses biologically active molecules such as polypeptides. However, the specification asserts no purpose for the delivery of any complex which does not comprise a nucleic acid, and does not clearly contemplate the delivery of any biologically active polymer other than a nucleic acid. The specification fails to teach one of skill in the art how to make or use complexes which do not contain nucleic acids, and it is unclear how molecules such as biologically active polypeptides are to be used in the invention. Furthermore, it is unclear how complexes comprising biologically active polypeptides can be prepared such that the proteins retain their activity. On the other hand, all of the working examples disclosed in the specification concern complexes comprising DNA, and the delivery of biologically active nucleic acids to cells (see pages 22-29), and much of the specification is dedicated to making and using complexes comprising DNA as a biologically active molecule. In particular, page 1-4 generally discuss the characteristics of condensed DNA, and the importance of condensation for gene delivery in vivo (see sentence bridging pages 1 and 2), and the summary at page 5, lines 7-10 describes the invention as "particles containing an excess of DNA". For these reasons, the specification has not enabled the use of any complex which does not comprise a

nucleic acid, and has not enabled the delivery of any biologically active polymer other than a nucleic acid.

The delivery of nucleic acids to cells *in vitro* has readily apparent uses, such as the expression and subsequent purification of desirable polypeptides. The specification teaches working examples of the use of the invention for delivery of nucleic acids to cells *in vitro*, and is fully enabled for this use.

With respect to the delivery of nucleic acids *in vivo*, the specification provides a working example of the delivery of a plasmid encoding reporter enzyme, but fails to teach or assert any useful purpose for this process. On the other hand, the specification contemplates the use of the invention in gene therapy. See page 14, lines 14-19. Additionally, claims 15-18 are drawn to a drug for delivery to a cell *in vivo* or *in vitro*. The specification does not contemplate the use of any compound as a drug other than a nucleic acid. For this reason, the specification is required to enable claims 15-18 for gene therapy to the extent that these claims read on delivery to cells *in vivo*.

At the time the invention was made, successful implementation of gene therapy protocols was not routinely obtainable by those skilled in the art. This is reflected by three recently published reviews. Orkin (Report and Recommendations of the Panel to Assess the NIH Investment in Research on Gene Therapy, 1995) teaches that "significant problems remain in all basic aspects of gene therapy. Major difficulties at the basic level include shortcomings in all current transfer vectors and an inadequate understanding of the biological interaction of these

vectors with the host" (page 1, item 3). Orkin teaches that problems exist in delivering nucleic acid sequences to the appropriate target cell or tissue and achieving the appropriate level of expression within that cell or tissue (page 9). Verma et al (1997) teach that "there is still no single outcome that we can point to as a success story (p. 239, col 1). The authors state further, "Thus far, the problem has been the inability to deliver genes efficiently and to obtain sustained expression" (p.239, col. 3). Anderson (1998) states that "there is still no conclusive evidence that a gene-therapy protocol has been successful in the treatment of human disease" (p. 25, col. 1) and concludes, "Several major deficiencies still exist including poor delivery systems, both viral and non-viral, and poor gene expression after genes are delivered" (p.30).

The instant invention addresses the issue of nucleic acid delivery, but does not address the problems associated with gene expression in any way. The specification provides a working example of the intravenous delivery of a reporter gene and its subsequent expression in various tissues of a mouse, but provides no working example of gene therapy, nor any guidance which would allow one of skill in the art to improve gene expression sufficiently to enable the practice of gene therapy as generally encompassed by the claims. The specification teaches that therapeutic nucleic acids may be delivered by any one of a wide variety of routes. See page 17, lines 4-22. However, the specification fails to identify any specific gene which could be used to treat any specific disease, and provides no guidance as to the dosages or administration profiles required to treat any disease. In addition, the results presented in Table 1 on page 27 do not provide convincing evidence that the instant invention improves DNA delivery relative to any existing

technique employed in gene therapy, because there is no comparison to any known technique, the sample size is extremely small (13 animals), and there is no apparent control experiment or statistical analyses. Because the existing delivery and expression techniques cannot be used to predictably treat diseases (see Orkin, Verma, and Anderson above), it is necessary for the specification to provide guidance to the skilled artisan as to how to overcome the factors which hamper gene delivery and expression such that a therapeutic result is achieved. It is noted that because the claims encompass gene therapy generally, the scope which must be enabled is very broad and includes the treatment of any disease with any gene. Because the specification fails to teach one of skill in the art how to select any gene for the treatment of any disease, or how to overcome the art-recognized problems associated with therapeutic gene delivery and expression, one of skill in the art would have to perform undue experimentation in order to use the invention commensurate in scope with the claims. It is further noted that the results set forth in Table 1 are confusing because, while the specification describes an experiment employing DNA/PEI/DS particles and refers to results in Table 1, Table 1 makes no mention of DS. Rather, Table 1 presents results for DNA/PEI/PAA complexes, and the specification does not appear to define the term "PAA".

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-7 and 12 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-7 are indefinite because the method steps are not concordant with the purpose set forth in the preamble. The claims are drawn to a method of delivering a complex to a cell, but there is no step which requires delivery of the complex to a cell.

Claims 5 and 12 are indefinite because they recite "the polyanion" without antecedent basis.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 8 and 11 are rejected under 35 U.S.C. 102(b) as being anticipated by Nicolau et al (Biochim. Biophys. Acta 721(2): 185-190, 10/1982).

Nicolau teaches a complex comprising plasmid DNA encapsulated by neutral liposomes, and its use in delivering the lipids and plasmid DNA to a cell. The neutral liposomes consist of phosphatidylcholine, a lipid which comprises a single negative charge and a single positive charge. See abstract; page 187, column 2, lines 3 and 4 of first full paragraph; and Table 1, page 188,

section A of the Table. Phosphatidylcholine lipids are considered to be polyions because they comprise two charges. This is consistent with the definitions of polycations and polyanions at page 12, lines 21-23 and 25-27 of the specification. The plasmid DNA is considered to be a charged polymer and a polyanion. Because the liposomes are electrically neutral, the complex of liposomes and nucleic acids must have the same net charge as the nucleic acids.

Thus Nicolau anticipates the claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 8-11 and 15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Nicolau et al (Biochim. Biophys. Acta 721(2): 185-190, 10/1982) in view of Vitiello et al (Gene Therapy 3(5): 396-404, 5/1996).

Nicolau teaches a complex of nucleic acids encapsulated by neutral liposomes, and its use in delivering the lipids and plasmid DNA to a cell. The neutral liposomes consist of phosphatidylcholine which comprises a single negative charge and a single positive charge. These lipids are considered to be polyions because they comprise two charges. This is consistent with

the definitions of polycations and polyanions at page 12, lines 21-28 of the specification. The plasmid DNA is considered to be a charged polymer. Because the liposomes are electrically neutral, the complex of liposomes and plasmid DNA must have the same net charge as the plasmid DNA. See abstract; page 187, column 2, lines 3 and 4 of first full paragraph; and Table 1, page 188, section A of the Table. Nicolau does not teach a charged polymer comprising a polycation, or a polycation attached to a polyanion.

Vitiello teaches that complexing nucleic acids with polylysine improves liposome-mediated gene transfer into cells. See abstract.

It would have been obvious to one of ordinary skill in the art at the time of the invention to add the polycation polylysine to the plasmid DNA of Nicolau. One would have been motivated to do so because Vitiello teaches that condensing DNA with a polycation prior to encapsulation by liposomes improves delivery to cells. Although Vitiello used cationic liposomes rather than neutral liposomes, one of skill in the art would reasonably expect to improve encapsulation efficiency in neutral liposomes because condensation of the plasmid DNA should allow encapsulation of more molecules per unit volume. Claim 15 is included in this rejection because a neutral liposome comprising a DNA polycation meets the limitations listed in a) and b) of claim 15, and because it is readily apparent that the liposome can be delivered to a cell *in vitro* for an enabled purpose such as the production and subsequent purification of an encoded protein. For the purpose of examination under 35 U.S.C. 103, the therapeutic implications of the preamble term "drug" are accorded no patentable weight.

Thus the invention as a whole was prima facie obvious.

Claims 10 and 16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Nicolau and Vitiello as applied to claims 8-11 and 15 above, and further in view of Baker er al (Nucl. Acids Res. 25(10): 1950-1956, 5/1997).

The teachings of Nicolau and Vitiello are discussed above. Briefly. These references can be combined to teach a complex for delivery of a polyion to a cell, wherein the complex comprises a DNA/polycation complex encapsulated in phosphatidylcholine liposomes. The polycation is PLL. Phosphatidylcholine is considered to be a polyion because it comprises more than one charge, and it is considered to be a negatively charged polyion because one of these charges is negative. These references do not teach the use of PEI as a polycation.

Baker teaches that PEI may be substituted for PLL as a condensing agent in transfection complexes. See last sentence of abstract.

It would have been obvious to one of ordinary skill in the art at the time of the invention to substituter PEI for the PLL of Nicolau and Vitiello. One would have been motivated to do so because Baker teaches that PEI performs the same function as PLL, and because substitution of PEI for PLL resulted in increased transfection efficiency.

Thus the invention as a whole was *prima facie* obvious.

Claim 14 is rejected under 35 U.S.C. 103(a) as being unpatentable over Nicolau and Vitiello as applied to claims 8-11 and 15 above, and further in view of Soon-Shiong et al (US Patent 5,545,423, issued 8/23/96).

The teachings of Nicolau and Vitiello are discussed above. Briefly. These references can be combined to teach a complex for delivery of a polyion to a cell, wherein the complex comprises a DNA/polylysine complex encapsulated in a neutral liposome. These references do not teach a pegylated derivative.

Soon-Shiong teaches that PEG derivatization of polylysine enhances the biocompatibility of microcapsules containing polylysine. See column 3, lines 17-19.

It would have been obvious to substitute the PEG-derivatized polylysine of Soon-Shiong for the polylysine of Vitiello in the method disclosed by Nicolau and Vitiello. One would have been motivated to do so because Soon-Shiong teaches that derivatization of polylysine with PEG can increase the biocompatibility of microspheres associated with the polylysine. The resulting nucleic acid/PEG-PLL complexes could be considered to be a polyanion comprising a pegylated derivative.

Thus the invention as a whole was *prima facie* obvious.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner(s) should be directed to Richard Schnizer, whose telephone number is 703-306-5441. The examiner can normally be reached on Mondays and Thursdays between the hours of 6:20 AM and 3:50 PM, and on Tuesdays, Wednesdays and Fridays between the hours of 7:00 AM and 4:30 PM (Eastern time). The examiner is off every other Friday, but is usually in the office anyway.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Karen Hauda, can be reached at 703-305-6608. The FAX phone numbers for art unit 1632 are 703-308-4242 and 703-305-3014.

Inquiries of a general nature or relating to the status of the application should be directed to the group receptionist whose telephone number is 703-308-0196.

Richard Schnizer, Ph. D.

Karen M. Hauda

KAREN M. HAUDA
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600